

Importance of Chirality in Drug Therapy and Pharmacy Practice: Implications for Psychiatry

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Abstract

The implications of stereoselective pharmacokinetics and pharmacodynamics of chiral drugs is not only a curious scientific phenomena but has wide ranging implications in practical therapeutics, health care, and pharmacy and psychiatry practice. The impetus to market stereochemically pure "homochiral" drugs reinforces the need of pharmacists to educate themselves regarding issues of chirality and therapeutic decisions. Patient education and counseling should include the therapeutic advantages (reduction) in drug load, and in possible adverse effects. Choices made between homochiral and racemic drugs are not clear-cut and therefore policies and procedures in therapeutic review committees should begin to address these issues. This article reviews the concept of chirality and the stereoselective nature of drug action, and its impact on pharmacotherapeutics.

Asymmetric organic molecules have long been known, however, the pharmaceutical implications of racemic drugs have only been extensively recognized in the last 20 years.^{1–4} Advances with regard to structures of various sites of drug action and improvements in methods for synthesizing and analyzing stereochemically pure drugs has resulted in increased interest in marketing of individual pure enantiomers of chiral drugs. In the future, more stereochemically pure drug agents will become clinically available and pharmacists

will be relied upon for their knowledge and expertise in this area.

This article provides an overview of stereochemical concepts of chirality. The impact of chirality on psychiatric medications has implications for clinical practice as numerous psychiatric drugs, particularly antidepressants, have one or more chiral centers. A heightened awareness of the stereoselective lexicon, and the stereoselective nature of pharmacokinetics and pharmacodynamics are therefore necessary.

STEREOCHEMICAL ASPECTS OF DRUG ACTION

Terminology

The most common example of chirality is that due to an sp³-hybridized tetrahedral carbon atom to which four different substituents are attached (Figure 1). This molecule does not have a plane

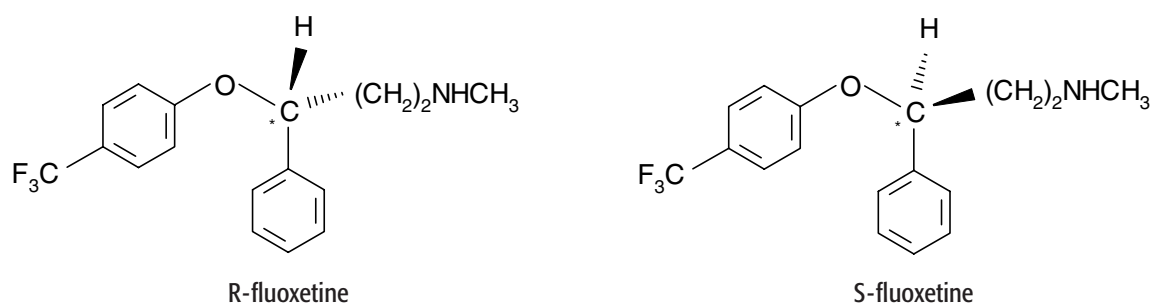
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**FIGURE 1**

Enantiomers of fluoxetine *Denotes chiral center

of symmetry and is called a chiral molecule. A drug such as the anti-depressant fluoxetine, has one chiral carbon, and therefore exists as a pair of isomers, which are not superimposable “enantiomers”, or opposite drugs called enantiomers, which are mirror images of each other. Fluoxetine is currently marketed in most countries as a racemate or a 50:50 composite of both of its enantiomers.

In the past, the relative configuration of enantiomers has been described using the *d* or (+) and *l* or (–) nomenclature. The enantiomers of fluoxetine have identical physicochemical properties to each other (ie, melting point, solubility). However, the direction in which they rotate plane-polarized light differs. This difference has led to the system for characterizing enantiomers. An enantiomer that rotates light clockwise or counterclockwise is said to be dextrorotatory [*d* or (+)], or levorotatory [*l* or (–)], respectively. Optical activity refers to the rotation of a plane of polarized light and enantiomers are often called optical isomers. A racemate is a 50:50 composite of enantiomers of drugs that will not appear to rotate plane-polarized light and is denoted as [±] (Table 1).

The Cahn, Ingold, and Prelog nomenclature is now employed to assign absolute configuration of the molecular structure of chiral tetrahedral molecules.⁵ The stereochemical orientation of ligands in space depends on mass assignments of respective enantiomers is designated by the descriptors *R* (rectus or clockwise rotation) and *S* (counterclockwise

or sinister). In addition, the rotation of polarized light is generally followed. There is no relationship between the system of nomenclature to describe absolute configuration (such as *R* and *S* assignment) and the direction in which one enantiomer will rotate plane-polarized light [eg, (+) or (–)].

Additionally, it should be recognized that elements other than carbon, such as sulfur and phosphorus, could act as chiral centers. The chiral

TABLE 1

Examples of Chiral Drugs from Various Therapeutic Classes

Antiarrhythmics	Propafenone, tocainide
Antibiotics	Ofloxacin, moxalactam
Anticoagulants	Warfarin, acenocoumarol
Anesthetics	Prilocaine, ketamine, pentobarbital
Antiemetics	Ondansetron
Antihistamine	Terfenadine, loratadine
Antihyperlipidemic	Atorvastatin
Antineoplastics	Cyclophosphamide, iphosphamide
Antimalarials	Chloroquine, halofantrine, mefloquine
Muscle relaxants	Methocarbamol, baclofen
NSAIDS	Ibuprofen, ketorolac
β-blockers	Propranolol, metoprolol
β-adrenergics	Salbutamol, terbutaline
Calcium channel blockers	Verapamil, nimodipine
Opiate analgesics	Methadone, pentazocine
Proton pump inhibitors	Omeprazole, pantoprazole, lansoprazole

carbon atom is predominant in pharmaceuticals; however, cyclophosphamide and sulindac are examples of racemates with a chiral phosphorus and sulfur heteroatom, respectively. The structure of cyclophosphamide has a four-covalent chiral phosphorus atom and sulindac has a three-covalent sulfoxide group.

Further, it is possible for molecules to have more than one chiral center. Labetalol has two chiral

centers and a maximum possibility of 2^n optical isomers or enantiomers, where n is the number of chiral heteroatoms in the molecule (Figure 2). Labetalol has four optical isomers, two pairs of enantiomers (R,S & S,R and R,R & S,S). However, there are compounds within this group of optical isomers that are not enantiomers. Compounds 1 and 3 and compounds 2 and 4 are not mirror images of each other and are called diastereomers. The

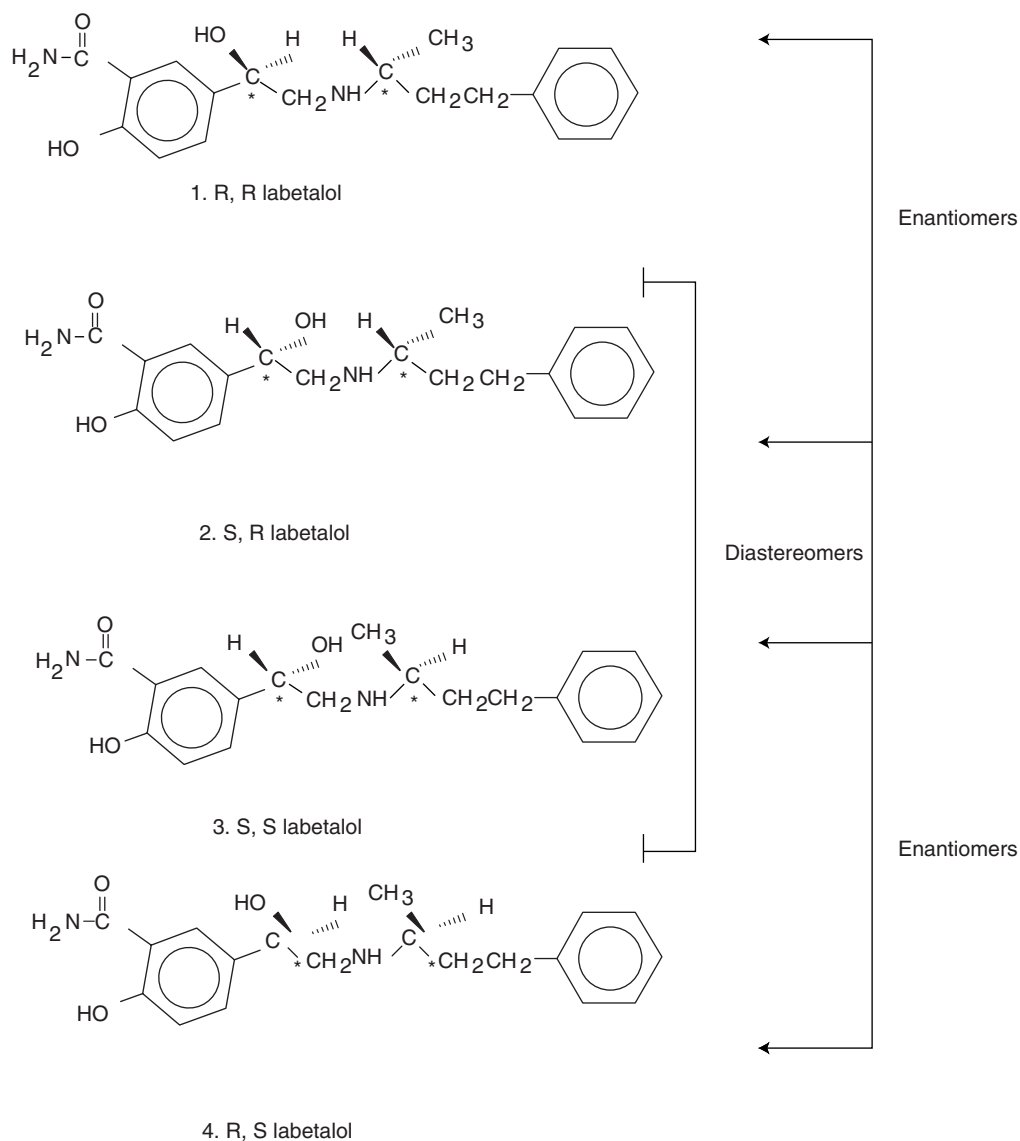


FIGURE 2

Stereochemistry of labetalol * Denotes chiral centers

term diastereomer can be confusing in that geometric isomers (eg, E and Z or cis and trans isomers) are also referred to as diastereomers (eg, doxepin) (Figure 3). Geometrical isomers arise from double bonds or cyclicity. In contrast to enantiomers, diastereomers can differ in their physiochemical properties to one another including solubility, stability and compatibility.

Chirality is not limited to tetrahedral centers and geometric isomerism, but exists due to restricted rotation such as steric hindrance. Examples of this include: planar chirality, axial chirality, helicity, torsional chirality or topological asymmetry, and organometallic complexes. Atropisomers (eg, gossypol) are an example of a drug that possesses restricted rotation chirality.

Chiral xenobiotics may lack configurational stability. The potential exists for some chiral drugs to undergo enzymatic or non-enzymatic interconversion of the enantiomers. Isomerization or enantio-merization is the conversion of one stereoisomeric form into another (ie, R-ibuprofen to S-ibuprofen) When isomerization occurs by the change of configuration at a single chiral center, the process is called epimerization, and when it leads to the formation of a racemate it is termed racemization. Non-enzymatic inversion of drugs is important in the pharmaceutical manufacturing process and has implications for the shelf life of a drug and the economic feasibility of the resolution. (ie, thalidomide and ketorolac)

Racemization may also occur in physiological fluids, such as the exposure to the acidic environment of the stomach. Enzymatic inversion is concerned with inversion under physiological conditions. Under these conditions, enantiomers may be inverted with the outcome of a racemate enriched in one of the antipodes. Demonstration of metabolic chiral inversion may have profound consequences for the development of a new pharmaceutical entity. A better understanding of the factors facilitating such interconversion may greatly aid drug development by identifying this feature at an early stage, thereby reducing bioanalytical and toxicology workload. Given the possibility of chiral inversion of racemates and stereochemically pure enantiomers, regulatory agencies are increasingly asking for evidence regarding this phenomena following administration of racemates or single enantiomers.

The Importance of Chirality in Drug Molecules

Pharmacists are aware of chirality when a prescription is dispensed for levothyroxine, D-penicillamine or dexamphetamine. Most pharmacists would recognize that there are dextro and levo rotary forms of these compounds and that these drugs are stereochemically pure. Conversely, few may be aware that many other drugs are stereochemically pure (eg, sertraline, paroxetine, apomorphine). There were at least 486 drugs clinically

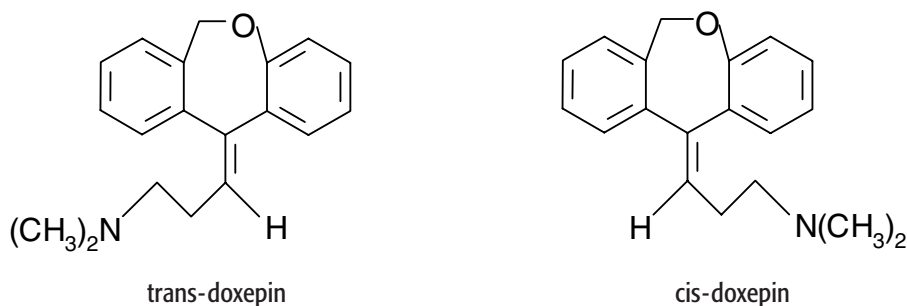


FIGURE 3

Geometric isomers of doxepinluoxetine

available for use in the United States in 1980 that were synthetic chiral pharmaceuticals. In a survey of 1850 drugs, of which 1327 were synthetically obtained, 528 contained one or more chiral centers of which, 88.4% were used as a racemate (Table 1).⁶ In general, natural products are normally chiral; however, racemates have been less expensive to chemically synthesize.

Pharmacological Difference Between Enantiomers

Qualitatively and quantitatively enantiomers may have similar or different pharmacological effects. This may be related to stereoselective pharmacokinetics or pharmacodynamics. The terms “eutomer” for the more potent isomer and “distomer” for the less potent one have been suggested.⁷ It is important to consider which pharmacodynamic effects are being considered when using the terms eutomer or distomer as they are usually employed to describe only the single most obvious effects. For example, S(-) timolol is marketed as a stereochemically pure enantiomer for hypertension.^{8,9} The S(-) enantiomer of timolol decreases intraocular pressure and is used in the treatment of glaucoma, although the R(+) enantiomer is also effective. The S(-) enantiomer applied to the eyes can cause β -adrenoreceptor bronchial blockade.^{10,11} Hence, the terms “eutomer” and “distomer” apply to both R and S timolol depending on which pharmacological effect is being examined.

No generalizations can be made concerning enantiomers since they exhibit a wide variation in effects. Examples of these effects consist of the following:

1. Equipotent enantiomers (eg, cyclophosphamide, flecainide).
2. One enantiomer with all or most of the activity (eg, NSAIDs, β -blockers).
3. Both enantiomers active with similar therapeutic and toxic effects but differ in magnitude (eg, warfarin).

4. Both enantiomers active but with quantitatively different therapeutic and toxic effects (eg, verapamil).¹²⁻¹⁴

Pharmacological Significance

Deoxyribonucleic acid (DNA) is composed of right-handed helices made of 2-deoxyribose monomer carbohydrates of the D- (or R-) configuration. Proteins and drug metabolizing enzymes, serum proteins, and transport proteins are composed of L- or usually S- (cysteine being the exception) amino acid monomers. The preferential interaction of one enantiomer of a racemate with chiral macromolecules within the body, leads to expressed pharmacokinetic and pharmacodynamic effects.^{2,15-17}

Enantiomers can be absorbed, distributed, metabolized, and excreted differently.¹²⁻¹⁴ Further, disease states, route of administration, genetic variability, and drug-interactions may be stereospecific. Enantiomers administered alone may have different actions within the body than a marketed racemate.^{1-4,15-18} It has been known for many years that opiate enantiomers can interact with different receptors, leading to different pharmacological effects.¹⁹ The (-) enantiomers of opiates are potent narcotic analgesics, whereas their (+) enantiomers are useful anti-tussive agents (eg, propoxyphene, dextromethorphan). Labetalol has multiple isomers that differ in α - and β -receptor blocking activity. The S,R isomer of labetalol is predominant for α -receptor blocking activity; the R,R isomer contributes most of the β -receptor blocking activity and this isomer known as dilevalol has been used as an anti-hypertensive agent.²⁰ The two other isomers may contribute to the drug's activity, but to a much lesser extent. While labetalol is unique among β -blocking drugs because of its α -adrenoreceptor activities is known, there is less awareness of its chiral features, or that its (R,R) isomer's hepatotoxic action prohibits its clinical use. However, this toxicity is not detected when the racemate drug is administered. It is unknown which isomer contained within labetalol

is hepatoprotective.²⁰ This example suggests that administration of a racemate, of a drug is akin to administering a drug combination that may be very different than administering these agents alone.

Stereochemically Pure Homochiral Drugs

With the great improvements in technical and economic feasibility in stereospecific synthetic and analytical methods, a central controversy in the therapeutic use of all racemic drugs, in particular the many NSAIDs, β -blockers, proton pump inhibitors and psychiatric agents, has become whether these drugs should be produced, marketed, remarketed, and used clinically as the racemate or as the single active enantiomer. Currently, there is intense debate between pharmaceutical scientists, pharmaceutical companies, and drug regulatory agencies on the relative merits of the clinical use of stereochemically pure enantiomers as opposed to racemates. The decision to market the stereochemically pure enantiomer of some drugs is clear. For example, the use of D,L dopa leads to granulocytopenia; however, the clinical use of the pure enantiomer L-dopa has not shown this adverse effect.²¹ It has been known that changing the enantiomeric composition of chiral drugs may affect the pharmacological profile.^{22,23} The R(-) enantiomer of indacrinone possesses diuretic activity and the S(+) enantiomer induces uric acid secretion. Through manipulation of the enantiomer ratio from a S(+)/R(-) 1:1 to a S(+)/R(-) 1:9 ratio for hypertensive patients, or those with congestive heart failure with normal uric acid levels is being considered for clinical practice. Increasing the amount of the S enantiomer for patients with gout may also have clinical utility.²²⁻²³

The following advantages provide an impetus towards efforts to develop pure drug enantiomers:

1. Separating unwanted pharmacodynamic side effects from toxic effects if these reside exclusively in one enantiomer.
2. Expose the patient to less body load and thus reduce metabolic/renal/hepatic drug load.

3. Easier assessment of physiology, disease, and drug co-administration effects.
4. Reduce drug interactions.
5. Avoid enantiomer-enantiomer drug interactions.
6. Avoid bioinversion.
7. Easier assessment of efficacy and toxicity through pharmacokinetic/pharmacodynamic monitoring of the stereochemically pure active enantiomer.

From the perspective of the pharmaceutical industry, commercially pure enantiomers, once developed, may be eligible for patent protection and market exclusivity.²⁴ However, the complexity of isolating and producing a pure enantiomer, as well as the expense of evaluating its efficacy and safety in accordance with regulatory standards, may make the cost prohibitive. Also, the technology for producing a pure enantiomer may not yet exist. For example, polycyclic non-aromatic molecules, studded with chiral centers, such as erythromycin, podophyllotoxin, and paclitaxel are all chiral compounds. All of these drugs are technically difficult, if not impossible, to resolve into homochiral pure enantiomers.

Additionally, some pure enantiomers are thermodynamically unstable; therefore it may be possible for a pure enantiomer to spontaneously racemize into a racemate [\pm R,S] mixture of enantiomers. Thalidomide is a former chiral sedative withdrawn from the market in the 1960s due to severe teratogenicity. However, there is renewed interest in restricted use of thalidomide because of its immunomodulatory and anti-inflammatory effects.

Thalidomide undergoes facile base-catalysed chemical racemization in aqueous media.²⁵⁻²⁸ It also appears that *in vivo* chiral inversion takes place mainly in the circulation and in albumin-rich extravascular spaces with a high concentration of albumin, while inversion is slower in more peripheral sites.^{27,28} A similar racemization phenomena has also been observed for a thalidomide analogue EM12 both *in vitro* and *in vivo*.^{29,30}

Chiral inversion of thalidomide is dependent on the medium employed and it would be misleading to draw conclusions about *in vivo* selectivity from *in vitro* studies. Putative differences in therapeutic or adverse effects of the thalidomide enantiomers would be abolished by rapid interconversion *in vivo* and render the development of a stereochemically pure enantiomer ineffective.

Stability and storage are also important considerations of a pure enantiomer, as shelf life may be different from the racemate and spontaneous racemization may limit the possibility of marketing the pure enantiomer.⁴

PHARMACY PRACTICE ISSUES

Therapeutic Drug Monitoring

Individualizing a patient's drug dosage to achieve a desired drug concentration within a desired range, has led to many therapeutic advances in a number of drugs.³¹ Clinical pharmacists should be aware that the chromatographic technology is available to separately measure the complete profile of chiral drug enantiomers.³² Measuring total plasma or urine drug levels of racemic drugs could lead to data misinterpretation.^{1,33} Indeed establishing concentration effect relationship with chiral drugs can be difficult and interpretation of drug levels based on the active enantiomer when the racemate is administered may assist in establishing and understanding of these relationships.

Drug Interactions

Subtle effects may arise from drug interactions of a non-chiral drug with one that is chiral. Phenylbutazone is achiral, but inhibits metabolism of S(-) warfarin which is five times more potent than the R(+) form therefore decreasing its clearance and inducing enzymatic reduction of the R enantiomer.³⁴ Pharmacists should be aware of the possibility of stereoselective drug interactions.³⁵ Furthermore,

it is possible that some interactions with racemic drugs may not occur with homochiral drugs. If pharmacists are aware of this possibility, they may be better able to aid in the therapeutic outcome of patients.

Pharmacy and Therapeutics Committees

Regulatory agencies are considering the various issues arising from registration of single enantiomers. Pharmacy and therapeutic committees should also begin to approach the issues of chirality pragmatically. Formulary acceptance, whether for a racemate, single enantiomer, or combination of enantiomers, should be based on sound logical, scientific, and therapeutic reasoning. A pure enantiomer developed from a previously registered racemic drug should be submitted, treated, and evaluated as an application for a new drug to the formulary. Therapeutic economic risk/benefit aspects of enantiomer versus racemate must be judged separately for each drug.

The significant expenses associated with the development and manufacture of stereochemically pure drugs will add to their cost and there may be economic justifications for acceptance or rejection of a new therapeutic entity. It may not be economically feasible to pay an increased amount for only slightly increased efficacy.

Generic Drugs and Bioequivalence

Standardized international regulations regarding the use of enantiomers are not yet in place; however, regulatory guidelines are either present or under development in several countries throughout the world. The requirements for generic drugs must not be less in the case of enantiomeric substances than with non-chiral drugs.³⁶ When developing a generic racemic or stereochemically pure drug the product should possess similar enantiomeric composition to the trade name product. Drug substances quality specifications should include criteria for optical

purity of pure enantiomers. Also, limits of stereochemical impurities in homochiral drugs need to be defined.

Examples of stereoselective bioequivalence can be found; however, bioequivalence of racemic formulations is usually assessed non-stereospecifically.³⁷ The distinct possibility of pre-systemic metabolism or stereoselectivity in absorption, distribution, metabolism, or elimination could significantly affect racemate bioequivalence. No significant differences were found between two flurbiprofen formulations tested using non-stereospecific analysis. However, a stereospecific assay revealed a statistically significant difference in the area under the curve of the two products.³⁸ Another example includes ibuprofen in which formulations were bioequivalent when assessed non-stereoselectively, but showed a significant reduction in peak concentration of the active S-enantiomer when tested stereoselectivity.³⁹ Indeed, the pure enantiomer of ibuprofen may be absorbed faster than the corresponding racemate.⁴⁰ This phenomena may also occur for other pure enantiomers and should be considered *ab initio* in the drug development process as it may have clinical importance in terms of onset of drug action.

Pharmacist Patient Education

There are many issues related to appropriately educating patients by pharmacists that may need to be addressed as more “chiral switches” from racemates to pure enantiomers occurs.

The increased availability of stereochemically pure drug products may lead to increased drug information inquiries by patients. This would enhance the position of the pharmacist as drug information resource and as an educator of all the issues surrounding chirality of drugs. Moreover, the need to communicate, effectively counsel, and monitor patients will grow in importance as therapies become more complex if both racemates and pure enantiomers are available. Furthermore, developing

a standard set of chiral regulations will become important to avoid discrepancies in labeling or misinformation given to patients.

In addition, we have recently seen the remarketing of the racemic antihistamine loratadine as the pure enantiomer desloratadine and the racemic omeprazole as esomeprazole. Some representative examples of chiral drugs that may be marketed as stereochemically pure drugs in the near future pull (fluoxetine) and pharmacists should be aware that many other are in development.

Finally, pharmacists must exercise caution when evaluating literature regarding chirality. Misinformation and many omissions have been provided in previous literature reviews regarding stereochemical issues. For effective clinical practice pharmacists as the drug experts must be cognizant of the importance of chirality and be able to translate scientific data as well as clinical knowledge clearly and effectively to their patients and other members of the allied health care team.

Pharmaceutical Issues

Pure enantiomers may exhibit different solubility and dissolution from their corresponding racemates.⁴² There is also a possibility of preferential interaction of one enantiomer with supposedly inert chiral excipients, such as cellulose derivatives.⁴³ A chiral drug can interact with excipients to form diastereomers. This derivative may possess different physicochemical properties and result in stereoselective release of the drug from the formulation.⁴⁴ Thus, in compounding or preparation of racemates and enantiomers, “inert” excipients may lead to differences in release, dissolution, and absorption of individual enantiomers all of which could affect a drug’s pharmacokinetics and pharmacodynamics.

It must be recognized that chirality does not simply involve chiral carbon centers, and stability and compatibility may not be the same between enantiomers and the racemate. Furthermore, racemic solids can exist as racemic mixtures or conglomer-

ates, racemic compounds, or a racemic solid solution (pseudoracemate).⁴¹

Psychiatry Issues

Various drugs of neuropsychopharmacological importance contain one or more chiral centers (Table 2). For instance, the anti-depressants fluoxetine, venlafaxine and trimipramine are commonly prescribed racemates, as are the anti-psychotics thioridazine and the hypnotic zopiclone. Further-

more, chiral centers are also introduced during drug metabolism (ie, the formation of the chiral 9-hydroxyrisperidone from the achiral risperidone).

The individual enantiomers of chiral drugs used in psychiatry practice may differ markedly from one another with regard to interactions with cytochrome (CYP) P450 enzymes, elimination half-lives, binding to receptors and uptake sites, and pharmacological properties. Interestingly, for some drugs such as paroxetine, sertraline, and methotrimeprazine that have chiral centers it was decided by the

TABLE 2

Chirality and Drugs Used in Psychiatry from Various Therapeutic Classes.

Anticonvulsants/ Sedatives/ Hypnotics	Hexobarbital	Antiparkinson agents	Levodopa	Antidepressants	Bupropion
	Mephentyoin		Biperiden		Trimipramine
	Secobarbital		Trihexyphenidyl HCl		Reboxetine
	Mephobarbital		Procyclidine		Fluoxetine
	Pentobarbital		Orphenadrine HCl		Tomoxetine
	Thiopental		Ethoprazine		Nisoxetine
	Thiohexital		Femoxetine		
	Lorazepam		Molindone		
	Oxazepam		Venlafaxine		
	Camezepam		Tranlycypromine		
	Ketazolam		Viloxazine		
	Temazepam		Deprenyl		
	Zopiclone		Oxaprotiline		
			Mianserin		
			Nomifensine		
			Citalopram		
			Doxepin		
			Tianeptine		
			Mirtazapine		
			Milnacipran		
Antipsychotics	Butaclamol	Opioid dependency	Methadone	Stimulants	Methylphenidate
	Sulpiride				Amphetamine
	Mesoridazine				Fenfluramine
	Besylate				
	Thioridazine				
	Sulfuridazine				
Clopenthiol					

manufacturer to market the stereochemically pure enantiomer over that of the racemate.

It is probable that several "chiral switches" will occur and this may impact prescribing in psychiatry. For example, the selective serotonin reuptake inhibitor citalopram was originally marketed as the racemate but recently the active S-enantiomer (escitalopram) is now marketed in the United States and other countries.⁴⁵ It is suggested that by use of the pure S-enantiomer (escitalopram) adverse effects attributable to the R-enantiomer will be avoided and increased drug potency is apparent. Animal studies and studies in depressed patients suggest a relatively rapid onset of escitalopram compared to citalopram marketed as the racemate.⁴⁶⁻⁴⁷ Furthermore, the R-enantiomer but not the S-enantiomer is a substrate for CYP P4502D6 and hence genetic polymorphism and variability in drug concentrations would be avoided by marketing the S-enantiomer.⁴⁶⁻⁴⁷

Fluoxetine was also first developed, marketed, approved and used clinically as a racemate; however, development of both the R and S enantiomers has been ongoing. The S and R enantiomers were both being developed clinically as treatments for migraine and as an anti-depressant, respectively. S-fluoxetine appears to have several advantages over the racemic form including a reduced adverse effect profile, a better antidepressant response rate as well as a more rapid onset of action.⁴⁸ R-fluoxetine was being developed by *Sepracor* and demonstrated initial clinical promise of a reduced incidence of sexual dysfunction side effects, however, at higher doses cardiac adverse effects were noted and its development appears to be halted.⁴⁹

CONCLUSION

In the absence of consideration of stereochemistry, the growing body of pharmaceutical consequences of chirality would not have been interpreted correctly. A better understanding of the stereochemical issues of racemic drugs will aid their clinical use. Chemically and biologically, a racemate should not

be viewed as a single drug by pharmacists but as a 50:50 composite of two or more drugs.

Pharmacists serve society, as the profession responsible for the appropriate use of medicines to achieve optimal therapeutic outcomes.⁵⁰ Pharmacists, as the drug experts, should be aware of the clinical implications of chirality. Pharmacists have proven their ability to enhance patient outcomes in drug therapy with the emergence of patient-oriented services. The pharmacists' ability to provide pharmaceutical care will depend on their ability to educate themselves on the issues of chirality, and their willingness to assume greater responsibility in communicating with other health care professionals and patients regarding these issues.

Development of pure enantiomers is currently more economically feasible. Improved methods of analyzing and preparing enantiomers have also developed. Our mechanistic understanding of the chiral structure of sites of drug action is continually evolving. A continued interest in the commercial marketing of individual enantiomers will undoubtedly impact our clinical practice.

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